Cholangiocarcinomas can originate from hepatocytes in mice.

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Public Summary:
This study shows that mouse hepatocytes can give rise to intrahepatic cholangiocarcinomas (ICCs), a liver cancer previously believed to derive exclusively from biliary epithelial cells. Whether this lineage conversion also occurs in humans remains to be determined but seems possible, considering that liver diseases injuring hepatocytes carry an increased of ICC formation.

Scientific Abstract:
Intrahepatic cholangiocarcinomas (ICCs) are primary liver tumors with a poor prognosis. The development of effective therapies has been hampered by a limited understanding of the biology of ICCs. Although ICCs exhibit heterogeneity in location, histology, and marker expression, they are currently thought to derive invariably from the cells lining the bile ducts, biliary epithelial cells (BECs), or liver progenitor cells (LPCs). Despite lack of experimental evidence establishing BECs or LPCs as the origin of ICCs, other liver cell types have not been considered. Here we show that ICCs can originate from fully differentiated hepatocytes. Using a mouse model of hepatocyte fate tracing, we found that activated NOTCH and AKT signaling cooperate to convert normal hepatocytes into biliary cells that act as precursors of rapidly progressing, lethal ICCs. Our findings suggest a previously overlooked mechanism of human ICC formation that may be targetable for anti-ICC therapy.